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Neuromagnetic activity in the somatosensory cortices of children with cerebral palsy

Max J. Kurz[a,*], Tony W. Wilson[a,b,c]

[a] Department of Physical Therapy, Munroe-Meyer Institute for Genetics and Rehabilitation, University of Nebraska Medical Center, 985450 Nebraska Medical Center, Omaha, NE 68198-5450, USA
[b] Center for Magnetoencephalography, University of Nebraska Medical Center, Omaha, NE, USA
[c] Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE, USA

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ABSTRACT

Children with cerebral palsy (CP) have altered tactile, proprioceptive and kinesthetic awareness. These sensory impairments appear to be related to an aberrant organization of the somatosensory cortex. To date, the neuromagnetic responses of somatosensory cortices representing the foot have not been investigated in children with spastic diplegic CP. In this investigation, we used magnetoencephalography (MEG) to evaluate cortical differences in the earliest somatosensory responses elicited by foot stimulation in typically developing children and those with spastic diplegic CP who have a Gross Motor Function Classification Score of III–IV. All participants underwent unilateral tibial nerve stimulation of each foot as whole brain MEG data were acquired. Primary somatosensory cortical responses were modeled using an equivalent current dipole for each foot. The results presented in this study are the first to show that activation of the somatosensory cortices representing the foot in children with spastic diplegic CP is diminished, but not latent.

Almost 3.5 out of every 1000 children born in the United States have cerebral palsy (CP), and the prevalence of the disorder is on the rise worldwide [37]. Spastic diplegic is the most common type of CP [36], and typically results from perinatal defects or insults to white matter of the periventricular area of the brain [1]. This damage can promote a cascade of neurophysiological changes such as a reduction in the presence of glial cells, damage to sprouting axons, excessive apoptosis, and a reduction in the grey matter volume [12,25]. Altogether these changes impact the fidelity of the information that is transmitted along the thalamocortical tracts, which are essential for the adequate communication of sensory information to the cortices [11,31].

Several investigations have suggested that the immature brain of children with CP attempts to overcome these neurological deficits by rebalancing cognitive functions amongst the intact components of the brain throughout development [4,10,26,29,30]. For example, transcranial magnetic stimulation studies of children with CP have shown that the ipsilateral homologue cortices often assume the roles of the damaged contralateral cortices that would normally be involved in the control of a given limb's movement [4,10,26]. Additionally, it has been shown that the locations of the cortices that are involved in the control of the leg muscles are often more lateral in the homunculus like topology [31]. However, these changes in the organization and neural connectivity should be interpreted with caution because they are a result of competitive reorganization, which may not always be beneficial. For example, functional magnetic resonance imaging has shown that the decreased sensory perception seen in children with CP is most likely related to reorganization of the hand's representation in the somatosensory topology [2,35]. We suspect that similar changes are also present in the foot's somatosensory cortical representation, which may partly explain why these children lack the ability to perform skillful movement, and have poor motor control of their walking patterns.

High-density magnetoencephalography (MEG) is a relatively new, noninvasive, human quantitative neurophysiological imaging technique that provides the unique capacity to delineate active neuronal populations in both time and space. MEG provides a direct measure of neuronal activity by measuring the minute magnetic fields that are generated by local electrical exchanges in activated neuronal populations [5,9,14,34]. The technique is especially sensitive to activity in parallel-oriented pyramidal cells of the human cortex. A considerable amount of research has used MEG to quantify the activation and organization of the primary and secondary somatosensory cortex through the use of evoked magnetic field paradigms [8,15,17,20,23]. Outcomes from these studies have

* Corresponding author. Tel.: +1 402 559 9599.
E-mail address: mkurz@unmc.edu (M.J. Kurz).

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Table 1
Description of the participating children with cerebral palsy. AFO = ankle–foot orthosis.

	Subject age (years)	Gender	GMFCS	Type	Surgical history	Assistive mobility
1	11	Male	III	Spastic diplegic	Rectus femoris transfer Adductor release Psoas release	Forearm crutches Solid AFO
2	16	Female	IV	Spastic diplegic	Rectus femoris transfer Hamstring lengthening Rotational osteotomies	Power mobility Solid AFO
3	13	Male	III	Spastic diplegic	Rotational osteotomies Hamstring lengthening	Wheeled walker Solid AFO
4	15	Male	III	Spastic diplegic	None	Wheeled walker Articulated AFO

confirmed that the somatosensory cortex is organized into well-defined "homunculus" like boundaries (i.e., foot, arm, hand, leg, tongue, lips, etc.). Although these MEG techniques are well established, they have not been used to explore the functional integrity of the somatosensory cortex of children with CP. Exploring the somatosensory event-related fields (ERF) will further illuminate the neural mechanisms that are responsible for the motor control and sensory impairments seen in these children.

In this investigation, we examined the hypothesis that the somatosensory cortices that represent the foot would have reduced neuromagnetic responsiveness in children with CP. In particular we investigated the following novel questions: (1) Are the amplitudes of neuromagnetic responses for the foot lower in children with CP than their typically developing peers? (2) Is the latency of primary somatosensory responses longer in children with CP compared with matched controls?

The experimental paradigm used in this investigation was reviewed and approved by the University's Internal Review Board. Parental consent and child assent was obtained for four children with spastic diplegic CP (Age = 13.7 ± 2 years; 3 Males; 1 Female), and four sex- and age-matched typically developing children (Age = 13.5 ± 2 years; 3 Males; 1 Female). Children with CP were enrolled in the study if they were between 11 and 18 years of age, able to follow verbal instructions, had a Gross Motor Function Classification Score (GMFCS) between III and IV [21], did not have metal implants that would interfere with the MEG recordings, were not under Botulinum toxin A therapy within the last year, and had not undergone orthopedic surgery in the past nine months. Further details on the children with CP that participated in this study are provided in Table 1.

During MEG recording, children sat comfortably in a custom made nonmagnetic chair with their head positioned within the helmet-shaped sensor array. Unilateral electrical stimulation was applied randomly to the left or right tibial nerve within a single block with external cutaneous stimulators [15]. For each subject, more than 260 trials per foot were collected using an inter-stimulus interval that varied randomly between 600 and 800 ms. The electrical stimulation was a square wave pulse of 10 ms duration that was increased in amplitude until there was a noticeable flexion of the first phalange of the foot. Epochs were defined offline and were of 700 ms duration, including a 200 ms pre-stimulus baseline.

With an acquisition bandwidth of 0.1–330 Hz, neuromagnetic signals were sampled continuously at 1 kHz using a whole head 306-sensor MEG system (Elekta Neuromag, Helsinki, Finland) housed within a magnetically-shielded room. Prior to the MEG measurements, four coils were attached to the subject's head. A 3-D digitizer (Fastrak 3SF0002, Polhemus Navigator Sciences, Colchester, VT, USA) was used to determine the locations of these coils, three fiducial points, and the scalp's surface. Throughout the experiment, an electric current was fed to the coils, which allowed for the location of the coils relative to the sensors to be known at all times. Using MaxFilter (v2.1.15; Elekta), the MEG data from each condition and subject were transformed into a standard device-centered head position, individually corrected for patient head movements during the recording, and subjected to noise reduction using the signal space separation method with a temporal extension [27,28].

Artifact rejection was based on a fixed threshold method (MEG level > 2.0 pT), supplemented with visual inspection. Artifact-free epochs from each condition were time-domain averaged with respect to stimulus onset and then digitally filtered 0.1–120 Hz. For each participant, the 40 ms peak response (M40) to contralateral tibial nerve stimulation was modeled for each foot with a single equivalent current dipole (ECD) using the subset of sensors that covered both magnetic flux extremes (see Fig. 1). In all participants, the resulting ECD solutions met the 0.95 goodness-of-fit criterion for each foot. This MEG analysis method was also utilized in one of our previous studies of somatosensory cortex [33], which provides substantial methodological detail.

The respective source amplitudes and peak latencies of the M40 response were log-transformed before statistical analysis. The Kolomogrov–Smirnov tests confirmed that the log-transformed data sets were normally distributed ($p > 0.05$). Mixed-model ANOVA designs were used to probe for differences in the peak latency and source amplitude between groups and respective hemispheres. A 0.05 alpha level was used to determine significance. Statistical analyses were conducted in SPSS for Windows (Release 11.0.1), and all MEG pre-processing and source analyses used the Elekta Neuromag base software package implemented in Linux CentOS.

There was a significant between-group difference in source amplitude ($p = 0.02$; Table 2). Further inspection of the data indicated that responses from the somatosensory cortices were of lower amplitude in the children with CP (Figs. 1 and 2). Furthermore, the effect size of source amplitudes was quite large (Cohen's $d = 1.3$). There was no significant main effect of hemisphere (i.e.,

Table 2
Latency and source amplitude of the peak 40 ms somatosensory response to contralateral tibial nerve stimulation in typically developing children and children with cerebral palsy. SE = standard error (SE) of the mean.

Group	Latency (ms)		Amplitude (nAm)	
	Right hemisphere	Left hemisphere	Right hemisphere	Left hemisphere
Cerebral Palsy				
Subject 1	45.6	45.6	10.6	21.7
Subject 2	41.4	42.2	20.0	13.3
Subject 3	49.5	41.8	8.3	15.9
Subject 4	40.1	41.2	24.2	14.0
Mean ± SE	44.2 ± 1.6	42.7 ± 0.7	15.7 ± 2.6	16.2 ± 1.4
Typically developing				
Subject 1	48.2	47.3	35.2	30.2
Subject 2	44.2	50.1	23.8	19.2
Subject 3	43.0	43.0	49.6	39.4
Subject 4	45.0	44.0	18.9	24.5
Mean ± SE	45.1 ± 0.8	46.1 ± 1.2	31.9 ± 1.4	28.3 ± 3.2